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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,760	AUSTIN ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-66* is/are pending in the application.

4a) Of the above claim(s) *18-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 April 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 9/5/03. The amendment has been entered. Claims 1-17 have been previously cancelled. Claims 18-46 have been withdrawn from consideration as being drawn to a non-elected invention for the reasons of record. Claims 47-66 are examined herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Drawings

The drawings remains objected to, for the reasons of record. It is acknowledged that Applicants have indicated that formal drawings will be submitted upon receiving a Notice of Allowance.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 47-66 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for inhibiting the generation of active thrombin on the surface of a cell within a mammal wherein said method comprises directly administering to said cell a polynucleotide which encodes and expresses GRP78/BiP, whereby GRP78/BiP is produced in said cell and the generation of active thrombin on the surface of said cell is inhibited;

AND

A method for inhibiting the generation of active thrombin on the surface of a cell within an atherosclerotic plaque within a mammal wherein said method comprises administering to said cell interleukin-3, or interleukin- 10, whereby the generation of active thrombin on the surface of said cell is inhibited;

does not reasonably provide enablement for the full scope encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the method commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to methods for inhibiting the generation of active thrombin on the surface of cells in a mammal by "producing" an ER resident chaperone protein in atherosclerotic plaque cells, and encompass administering a compound or a nucleic acid encoding an ER resident chaperone protein to said cell. Therefore the nature of the invention is atherosclerosis therapy, and encompasses gene therapy.

The breadth of the claims

The broadest claims encompass "producing" an ER resident chaperone protein in atherosclerotic plaque cells in an animal by any method that results in producing an ER resident chaperone protein in the cells. Looking to the specification for guidance, it is clear that the claims encompass administering any compound which increases the level or expression of any ER resident chaperone protein or any compound which activates ER resident chaperone protein (see claim 47 and 60). Claim 61 indicates that the administered compound can be any cytokine. The broadest claims also encompass administering a nucleic acid which encodes and expresses any ER resident chaperone protein to the target cell, and encompasses any route of administration including systemic administration of the nucleic acid.

The unpredictability of the art and the state of the prior art

Regarding the administration of a nucleic acid encoding a gene of interest to a cell in a mammal (i.e. gene therapy), it is well established in the art that delivery is one of the key problems. For instance, regarding gene therapy in general, Anderson (Nature 1998; 392(suppl):25-30) teaches,

> The challenge is to develop gene therapy as an efficient and safe drug delivery system. The goal is more difficult to achieve than many investigators had predicted... The human body has spent many thousands of years learning to protect itself from the onslaught of environmental hazards, including the incorporation of foreign DNA into its genome. (See p. 25, second paragraph). The ultimate goal of gene therapy research is the development of vectors that can be injected, will target specific cells, will result in safe and efficient gene transfer into a high percentage of those cells, will insert themselves into appropriate regions of the genome (or will persist as stable episomes), will be regulated be either by administered agents or by the body's own physiological signals, will be cost effective and will cure disease. (See p. 30, first paragraph).

Crystal (Science 1995; 270:404-410) also indicates some of the problems associated with gene therapy in general, including problems associated with delivery. Specifically, regarding the obstacles of human gene transfer, Crystal teaches, "The [gene transfer] vector (should) be specific for its target, not recognized by the immune system..." (See p. 409, column 2 under "The perfect vector").

Regarding the delivery of gene therapy vectors to tumors, but applicable to the specific delivery of all gene therapy molecules, Greco (Frontiers in Biosci. 2002; 7:d1516-1524) teaches,

> The administration of gene therapy vectors requires that they be not only targeted, but also protected from degradation, sequestration or immune attack, in order to reach the appropriate sites for transfection. Although some success has been reported for naked DNA, efficient delivery has been restricted to intratumoral injection. (See p. 1517, paragraph bridging columns 1-2).

Therefore, Greco indicates that direct delivery of the nucleic acid to the desired site of transfection is critical for delivering the nucleic acid to the appropriate target cells.

Regarding the administration of a nucleic acid which encodes and expresses any ER resident chaperon protein in order to inhibit the generation of active thrombin on the surface of the cell, it is noted that the prior art does not teach that any ER resident chaperone proteins are associated with the generation of active thrombin on the surface of cells. Therefore, without evidence indicating a sufficient number of ER chaperone proteins can inhibit the generation of

active thrombin on the surface of a cell, it is unpredictable that any ER chaperone protein could inhibit the generation of active thrombin on the surface of a cell.

Regarding the administration any compound which increases the expression of any ER resident chaperone protein or any compound which activates ER resident chaperone protein, it is noted that the only compounds which has been identified by the prior art as capable of inducing the expression of an ER resident chaperone protein is interleukin-3, which has been shown to induce GRP78/BiP expression in cells (see Brewer, listed in the IDS as Citation No. 1). It is noted that the claims encompass administration of any cytokine in order to induce ER resident chaperone protein expression. However, the only cytokines which has been demonstrated to induce any ER resident chaperone protein expression are IL-3 and IL-10. Considering that cytokines are a diverse genus of molecules with extremely divers functions (such as pro-inflammatory cytokines and anti-inflammatory cytokines), it is highly unlikely that that all cytokines would induce ER resident chaperone expression. There is no indication in the relevant art that any compound or cytokine other than IL-3 (a pro-inflammatory cytokine) or IL-10 could induce expression of any ER resident chaperone protein. Therefore, without evidence explicitly indicating which compounds and cytokines activate the expression of ER resident chaperone proteins, it is unpredictable that any compound (or any cytokine other than IL-3 or IL-10) could activate expression of ER chaperone protein in a cell and inhibit the generation of active thrombin on the surface of the cell.

Additionally, as indicated above, the claims are very broad and encompass administering anything that "produces an ER resident chaperone protein" in the target cell. Furthermore, the specification clearly indicates, "Accordingly, any treatment, compound, protein, or

polynucleotide can be used that decreases the level of free calcium in the secretory pathway..." (See p. 16, lines 21-23). Therefore, the claims encompass administering any compound which decreases the level of free calcium in a cell, including calsequesterin. However, the prior art teaches that when calreticulin and calsequesterin were administered to an animal model for atherosclerosis, calsequesterin did not decrease plaque area (see Dai, abstract). Therefore, although the specification indicates that any compound which decreases the level of free calcium can be used in a method wherein the only contemplated use of the method is for the therapeutic treatment of atherosclerotic plaques, the prior art clearly indicates that not all compounds which decrease the level of free calcium in the secretory pathway, and specifically not calsequesterin, would not work as intended. Therefore, it is clear that additional experimentation is required in order to determine which calcium decreasing molecules would work in the claimed methods and which would not work.

Working Examples and Guidance in the Specification

The specification discloses that expression of recombinant GRP78/BiP (an ER resident chaperone protein) inhibits the generation of active thrombin on the surface of cells (in vitro). There is no disclosure indicating that any ER resident chaperone protein other than GRP78/BiP is capable of inhibiting the generation of active thrombin on the surface of a cell. Considering that ER resident chaperone proteins have different functions (such as Calcium regulation, protein folding, and protein transport) it is unpredictable which ER resident chaperone proteins could inhibit the generation of active thrombin on the surface of a cell.

There is no disclosure in the specification which overcomes the problems regarding gene delivery recognized in the art. Therefore, it is unpredictable that the nucleic acid of interest

could be administered by any means other than direct administration to the target cells and result in the transfection of the proper target cells. It is unpredictable that the nucleic acid of interest could be administered systemically to a mammal and result in the specific transfection of the target cells.

The specification does not disclose that any compound or any cytokine other than IL-3/IL-10 which can be used to activate the expression of any ER resident chaperone protein. Furthermore, the specification and the prior art (Brewer) indicate that IL-3 can activate the expression of GRP78/BiP.

Quantity of Experimentation

Considering the breadth of the claims, the unpredictable nature of the invention, and the limited guidance provided in the specification, additional experimentation would be required in order to practice the methods to the full scope encompassed by the claims. For instance, additional experimentation would be required to overcome the problems associated with systemic delivery of a nucleic acid to a target cell, additional experimentation would also have to be performed in order to determine if all ER resident chaperone proteins could inhibit the generation of active thrombin and if all cytokines could activate the expression of all ER resident chaperones (only a sufficient number of cytokines and ER resident chaperones would have to be demonstrated).

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the breadth of the claims, the unpredictable nature of the invention, the limited guidance provided in the specification and the high degree of skill required to practice the claimed methods, additional experimentation would be required in order to use the invention to the full scope encompassed by the claims. Based on the evaluation of all of the Wands factors, it is concluded that the amount of experimentation required to perform the broadly claimed invention is undue.

Response to Arguments

5. Applicant's arguments filed 9/5/03 have been fully considered but they are not persuasive.

Applicants note that the possibility of some experimentation, even if such experimentation is complex or extensive, may be required for the practice of the invention does not necessarily mean that the invention is not enabled (see p. 12 of the response).

Applicants argue that the specification provides a list of compounds which can be used to induce expression of ER resident chaperone proteins. Applicants also argue that methods have been disclosed for identifying compounds which induce the expression of ER resident chaperone proteins. Applicants contend that one of skill in the art can readily screen ***any*** compound for its ability to induce ER resident chaperone protein expression without undue experimentation. Furthermore, Applicants contend that the additional experimentation required would be routine to one of skill in the art (see p. 13 of the response).

In response, it is acknowledged that the specification provides a list of compounds which allegedly can be used to induce the expression of ER resident chaperon proteins in cells. It is respectfully pointed out that the specification does not indicate by example that all of the

compounds described in the specification do, in fact, induce expression of the desired proteins. Therefore, the specification merely indicates a laundry list of compounds which may or may not induce expression of ER resident chaperone proteins. It is respectfully pointed out that the specification indicates, "any treatment, compound, protein, or polynucleotide can be used that decreases the level of free calcium in the secretory pathway..." (See p. 16, lines 21-23). However, the prior art teaches that when calreticulin and calsequesterin (two molecules which decrease calcium levels) were administered to an animal model for atherosclerosis, calsequesterin did not result in the reduction of plaque size (see Dai, abstract), a result that should occur if calsequesterin increased the level of ER resident chaperone protein in the cell. Therefore, it is clear that additional experimentation is required in order to determine which molecules contemplated in the specification would work in the claimed methods and which would not work.

Applicants argue that they have disclosed a number of different ER resident chaperone proteins, including their amino acid and nucleic acid sequences and that the specification provides teachings regarding both viral as well as non-viral modes for delivering nucleic acid to cells in vivo. Applicants point out again that the specification sites over 39 references that allegedly provide more than ample evidence of success using viral and non-viral delivery systems. Applicants argue that liposomal formulations for delivering nucleic acids systemically were known to those of skill in the art. Therefore, Applicants contend, undue experimentation would not be required to carry out the claimed methods.

In response, it is acknowledged that the specification has disclosed the sequences of a number of different ER resident chaperone proteins. However, the issue is not whether the ER

resident chaperone protein have been described, but whether or not the ER resident proteins that have the desired effect have been identified. As previously indicated (and indicated above) the specification has only indicated by example one particular ER resident chaperon protein, GRP78/BiP, which can inhibit the production of active thrombin on the surface of a cell. Without a clear indication of which ER resident chaperone proteins inhibit the production of active thrombin on the cell surface, additional experimentation would be required before the claimed invention could be practiced.

Regarding Applicants arguments pertaining to gene delivery, it is acknowledged that the specification sites over 39 references related to gene delivery systems, and that liposomal formulations for delivering nucleic acids systemically were known to those of skill in the art. However, as previously indicated, there are specific problems recognized in the art with respect to systemic gene delivery. For instance, in order for the claimed invention to inhibit the production of active thrombin on the surface of a cell within an atherosclerotic plaque, the delivery method must be able to deliver the nucleic to the appropriate target cell: a cell in an atherosclerotic plaque. Direct delivery of the nucleic acid to the target cell is the only way to ensure that the nucleic acid is delivered to the appropriate target cell (see Greco).

In conclusion, it is acknowledged that additional experimentation does not necessarily mean that that the invention is not enabled. Enablement is determined based on an evaluation of the Wands factors, in their totality. In the instant case, consideration was given to all of the Wands factors, as indicated above, and it was determined that the amount of additional experimentation required to practice the claimed invention to their full scope would require an undue amount additional experimentation. That is, the nature of the invention (which includes

gene therapy), the breadth of the claims (any method of producing an ER resident chaperone protein in a cell in a plaque in an animal), the amount of guidance provided (relatively little considering the breadth of the claims), the working examples provided (one working example: GRP78/BiP), the state of the prior art (systemic delivery is unpredictable, not predictable that all calcium decreasing molecules will increase ER resident chaperone levels), the relative skill required (high), and the amount of experimentation required were all considered together in drawing the conclusion that an undue amount of additional experimentation is required in order practice the claimed invention ***to the full scope encompassed by the claims.***

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 47-54, 60 and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Hansson et al. (US Patent 5,208,019).

It is noted that the instant claims are very broad and encompass any method which "produces" an ER resident chaperone protein in a cell within an atherosclerotic plaque within a mammal. Looking to the specification for guidance, as well as the claims (see claim 61), it is

clear that the method can encompass administering a cytokine to plaque cells (see page 24, first paragraph). Therefore, the instant claim encompass any method for producing an ER chaperone protein in an atherosclerotic plaque cell, including administering a cytokine, such as gamma-interferon, to the target cells.

Hansson teaches a method wherein gamma-interferon is administered to an animal model for inhibiting the growth of cells in intimal lesions as well as in atherosclerosis (see column 3, lines 43-51). Considering that the instant claims do not set forth any limitations for the methods which can be used to produce an ER resident chaperone protein in the target cells, and also considering that the specification discloses that "IL-3 and other cytokines have been shown to induce the expression of ER chaperone proteins such as GRP78/BiP and GRP94" (see p. 17, first paragraph), the method of administering gamma-interferon, a cytokine, to an animal model for atherosclerosis (taught by Hansson) meets all of the limitations of the instant claims.

8. Claims 47-51, 53 and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Dai et al. (Ateriosclerosis, Thrombosis, and Vascular Disease 1997; Vol. 17:2359-2368).

It is noted that the instant claims are very broad and encompass any method which "produces" an ER resident chaperone protein in a cell within an atherosclerotic plaque within a mammal. Looking to the specification for guidance, it is clear that the method can encompass administering a chaperone polypeptide to the target cell (see p. 16 lines 4-24 and page 23, line 26-33). Furthermore, administering an ER resident chaperone protein to a cell would necessarily result in "producing" an ER resident chaperone protein in that cell. It is also noted that the

specification (see p. 16 lines 4-16) as well as claim 53 specifically indicate that calreticulin is an ER resident chaperone encompassed by the claims.

Dai teaches a method which comprises administering calreticulin (an ER resident chaperone, as indicated above) to the site of atherosclerotic plaque development (see abstract). Dai teaches that atherosclerotic plaque area is reduced in animals treated with calreticulin compared to controls (see abstract). It is noted that one of ordinary skill in the art would readily recognize that an atherosclerotic plaque would comprise endothelial cells, smooth muscle cells, macrophages and monocytes. Therefore, administration of calreticulin to the site of plaque development (as taught by Dai) meets all of limitations of the claim required to result in "producing an ER resident chaperone protein (and specifically, calreticulin) in a cell within an atherosclerotic plaque in an animal". The fact that the administration of calreticulin to the site of the plaque results in reduced plaque area is indicative that calreticulin was "produced" (e.g., delivered) to the cells of the plaque.

9. Claims 47-54, 60 and 61 rejected under 35 U.S.C. 102(a) as being anticipated by Mallat et al. (Circulation Research, 1999; vol. 85:e17-e24).

It is noted that the instant claims are very broad and encompass any method which "produces" an ER resident chaperone protein in a cell within an atherosclerotic plaque within a mammal. Looking to the specification for guidance, as well as the claims (see claim 61), it is clear that the method can encompass administering a cytokine to plaque cells (see page 24, first paragraph). Therefore, the instant claim encompass any method for producing an ER chaperone

protein in an atherosclerotic plaque cell, including administering a cytokine such as IL-10 to the target cells.

Mallat teaches a method wherein interleukin-10 (IL-10), a cytokine, is administered to an animal having atherosclerotic plaques resulted in a 60% reduction in lesion size (e.g., see abstract). Considering that the instant claims do not set forth any limitations for the methods which can be used to produce an ER resident chaperone protein in the target cells, and also considering that the specification discloses that "IL-3 and other cytokines have been shown to induce the expression of ER chaperone proteins such as GRP78/BiP and GRP94" (see p. 17, first paragraph), the method of administering IL-10, a cytokine, to an animal model for atherosclerosis (taught by Mallat) meets all of the limitations of the instant claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
Art Unit 1635

DAVE T. NGUYEN
PRIMARY EXAMINER